B

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/282,879	03/31/1999	SUBROTO CHATTERJEE	46906-2-DIV	9227

21874 7590 12/29/2005

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/282,879	CHATTERJEE, SUBROTO	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-17 and 32-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17 and 32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-16-05 has been entered.

Claims 13-17, 32-37 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 9-16-05, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Examiner has withdrawn the previous rejection under 35 U.S.C. 112, 2nd paragraph in view of persuasive arguments and pointing out the support for said phrases in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-14, 34 and claims 15-17 and 35-37 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13, 14 and 34 all recite the phrase "represented by SEQ ID NO:2". It is not clear to the Examiner as to what

Applicants mean by "represented by", i.e., whether the amino acid sequence of the enzyme used is indeed SEQ ID NO:2 or whether SEQ ID NO:2 is defined as "to stand for", to symbolize" etc. Examiner also notes that the sequence of the enzyme need not be identical to SEQ ID NO:2 to be represented by SEQ ID NO:2. Examiner suggests deletion of the phrase and referring the amino acid sequence directly as "having an amino acid sequence SEQ D NO:2". Correction is required

Claim 13 and claims 15-17 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 recites the phrase "is at least 70% identical to". It is not clear to the Examiner as to in what aspects said protein is 70% identical to the protein of SEQ ID NO:2. It is not clear to the Examiner whether applicants are referring to activity. amino acid sequence or any other aspect or characteristic of the protein. Since applicants have already made one reference to the activity, it appears that applicants are now referring now to the amino acid sequence. If that is so Examiner suggests applicants to amend the claim to recite "wherein said polypeptide has an amino acid sequence that is at least 70% identical to...".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 15-17, and 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound useful in the

diagnosis or treatment of a human neutral sphingomyelinase related disorder comprising binding a sphingomyelinase cleavage target to a solid support and contacting said solid support with a pharmacological agent and a recombinant neutral sphingomyelinase having an amino acid sequence SEQ ID NO:2 does not reasonably provide enablement for such a method in which the neutral sphingomyelinase comprises a fragment comprising 30 , 50 or 70 amino acids of SEQ ID NO:2 having at least about 50% of the neutral sphingomyelinase activity of SEQ ID NO:2 or wherein said sphingomyelinase has an amino acid sequence that is at least 70% identical to SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 13, 15-17, and 32-33 are so broad as to encompass a method of use of any variants or mutants of SEQ ID NO:2 comprising 30, 50 or 70 amino acids of SEQ ID NO:2 wherein said variants has at least 50% activity of the sphingomyelinase comprising SEQ ID NO:2 or any sphingomyelinase having an amino acid sequence that is at least 70% identical to SEQ ID NO:2 for identifying a compound useful in diagnosis or treatment of human sphingomyelinase disorder. The scope of the claims is not commensurate with the enablement

provided by the disclosure with regard to the extremely large number of sphingomyelinases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence to obtain the desired activity requires a knowledge of and guidance with regard to which specific amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single sphingomyelinase. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides with said function/activity. The specification is limited to teaching the use of SEQ ID NO: 2 as a sphingomyelinase but provides no guidance with regard to the making of variants, mutants, derivatives or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides for use in the above claimed method, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the polypeptides for the method encompassed by this claim.

While recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, the positions (i.e., amino acid residues) within a protein's sequence where amino acid

modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses the making and using of all polypeptides derived from SEQ ID NO:2 wherein said variants or mutants of SEQ ID NO:2 comprise 30, 50 or 70 amino acids of SEQ ID NO:2 and wherein said variants has at least 50% activity of the sphingomyelinase comprising SEQ ID NO:2 or the making and using of all polypeptides having 70% amino acid sequence identity with SEQ ID NO:2 (i.e., amino acid sequence with 70% identity to the enzyme of SEQ ID NO:2) because the specification does not establish: (A) regions of the protein structure which may be modified without affecting sphingomyelinase activity; (B) the general tolerance of sphingomyelinases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in SEQ ID NO:2 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including sphingomyelinases with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of sphingomyelinases required for the above method having the desired biological

characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action applicant disagrees and maintains that the disagreement is for the same reasons already made of record and the issue has been addressed in the instant submission. Applicant submits that they have deleted the term "derivative". Applicant also notes that Office has deemed that the method is enabling for the use of fragment of sphingomyelinase. However, Examiner has revised that earlier view and has now rewritten the rejection. This is because of the "comprising " language used in the claim. While the method is directed to the use of fragment, the fragment comprises any 30, 50 or 70 amino acids of SEQ ID NO:2 and therefore Examiner has now taken the position that the specification does not enable such fragments. Furthermore, since applicants continue to maintain that sphingomyelinases having an amino acid sequence that is at least 70% identical to SEQ ID NO:2 can be used in the claimed method, Examiner continues to maintain the rejection.

Claims 13 and 15-17, 32-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13 and 15-17, 32-33, are directed to a method of use of sphingomyelinase polypeptide comprising fragments of 30, 50 or 70 amino acids of SEQ ID NO:2 and having at least 50% activity of SEQ ID NO:2. Claims 13 and 15-17, 32-33 are rejected under this section

of 35 USC 112 because the claims are directed to a method of use of a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, (i.e., comprising any 30, 50 or 70 amino acids of SEQ ID NO:2) that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the genus of polypeptides for use in the claimed method. The specification does not contain any disclosure of the structure of all the polypeptide sequences comprising fragments of 30, 50 or 70 amino acids of SEQ ID NO:2 and having at least 50% activity of SEQ ID NO:2, within the scope of the genus for use in the claimed method. The genus of polypeptides for use in the claimed method is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species (i.e., SEQ ID NO:2) of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the above rejection, applicants have traversed arguing that claims satisfy the written description requirement. Applicants argue that as pointed in the appeal brief and prior response, practice of the invention is not limited to any particular N-Smase as long as it can

provide acceptable function. Applicants also argue that the polynucleotide encoding a sphingomyelinase has already been allowed in a sister patent wherein, said polynucleotide encodes a fragment. Examiner respectfully disagrees that such an argument is persuasive to overcome the above rejection. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the polypeptide for use in the claimed method includes species which are widely variant in structure. The genus is structurally diverse as it encompasses polypeptides which comprise any 30, 50 or 70 amino acids of SEQ ID NO:2 and the structure of rest of the amino acid sequence is unknown or not described (in the alternative fragments consisting of 30, 50 or 70 amino acids wherein said

fragments have sphingomyelinase activity would be more appropriate). As such, neither the description of the structure alone or function alone present in all members of the genus is not sufficient to be representative of the attributes and features of the entire genus.

With respect to the allowed claim in the sister patent it must be noted that claim is drawn to a polynucleotide sequence whose structure and function is described as opposed to either the structure alone or function alone as in instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-17 and 32-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chatterjee et al. (J. Biol. Chem., 1989, Vol. 264(21):12554-12561), Ausubel et al. (Current Protocols in Molecular Biology, John Wiley and Sons, 1987, pages 10.0.3-10.0.6). Ogita et al. (WO 9518119, 7-6-1995) and Taki Takao et al. (Anal Biochem., Jan. 1995, Vol. 224:490-493, cited in the IDS) or Malmqvist, et al.1981 (Zentralblatt fuer Bakteriologie, Mikrobiologie und Hygiene, Abteilung 1, Supplemente (1981), 10(Staphylococci Staphylococcal Infect.), 253-9). Claims 13-17 and 31 in this instant application are drawn to a method of identifying a compound comprising binding sphingomyelinase cleavage target (such as sphingomyelin) to a solid support, contacting the solid support with or without a candidate agent and a recombinant sphingomyelinase enzyme comprising SEQ ID NO:2, followed by

incubating under conditions whereby the sphingomyelinase cleaves the cleavage target to yield a product and the presence of the cleavage product is detected and compared between the two reactions, wherein a reduced concentration of the cleavage product relative to the control mixture that does not contain the agent identifies the candidate agent as a compound potentially useful in the treatment of human neutral sphingomyelinase related disorder.

Chatterjee et al. teach an assay method for the activity of neutral sphingomyelinase wherein a mixture of sphingomyelin is treated with the enzyme sphingomyelinase under conditions wherein the substrate is cleaved and cleaved product, ceramide is detected (see page 12555, 2nd column). Chatterjee et al. also teach that sphingomyelinase catalyzes the hydrolysis of sphingomyelin to ceramide and phosphorylcholine at both acidic and neutral pH. The reference also teaches that the study of neutral sphingomyelinases are necessary in view of its involvement in gentamicin-mediated nephrotoxicity in man and also due to the involvement of sphingosine, released as a consequence of the action of sphingomyelinase, in a cascade of reactions leading to the regulation of protein kinase C activity (see page 12554, Introduction). Thus it appears that the substrate, cleavage product and the importance of the sphingomyelinase reaction was common knowledge in the art. However, while the above reference teaches a purified SM and an assay for its activity, it does not teach a recombinant SM or the use of recombinant SM in an assay for detection of a pharmacological agent as claimed above even though the activity assay for the purified enzyme could be used for the same.

Ogita et al. teach the manufacture of a sphingomyelinase inhibitor obtained from a microorganism and its use to treat a variety of diseases and disorders such as HIV, diabetes, leukemia, cachexia etc. Ogita et al. also teach an assay for determining the inhibitory activity of

a compound using sphingomyelinase isolated from a rat brain wherein the assay is performed at a pH of 7.5 very close to the neutral pH. However, both the above references do not teach step of binding the cleavage target to a solid support or the use of recombinant SM.

Takao et al. specifically teach an assay for determining the activity of sphingomyelinase by immobilizing the cleavage target of the enzyme, namely, sphingomyelin, on to a solid support, a membrane followed by contacting the immobilized target with the sphingomyelinase enzyme and determine the cleaved product and correlate it to the activity of the enzyme. However, this reference also does not teach as to how to use the same assay for identifying compounds which modulate the activity of the enzyme.

Malmqvist et al. teach a method of assaying sphingomyelinase activity by using immobilized sphingomyelin on a solid support. The reference teaches the immobilization of the target on to octyl-Sepharose gel support and that stock gel of the immobilized lipid substrate could be stored for months and was easy to handle as a water suspension. However, this reference also does not teach how to use the same assay for identifying compounds which modulate the activity of the enzyme.

With the purified SM as taught by Chatterjee et al. and the knowledge existing in the art of protein biochemistry and molecular biology to make recombinant proteins as provided by Ausubel et al. and the importance of sphingomyelinase inhibitors as taught by Ogita et al., it would have been obvious to one skilled in the art at the time the invention was made to use the purified protein of Chatterjee et al., obtain a cDNA clone and make recombinant sphingomyelinase using the techniques of Ausubel et al. and use it to develop a method of identifying other compounds which inhibit sphingomyelinase on line with the method of Takao

et al. or Malmqvist et al. such that compounds identified could become useful in diagnosis or treatment of a human neutral sphingomyelinase related disorder. Chatterjee et al. teach that one of ordinary skill in the art would be motivated to do this in order to study the biochemical mechanisms involved in gentamicin-mediated nephrotoxicity or in Niemann-Pick disease and Ogita et al. teach that one of ordinary skill in the art would be motivated to do this because, when the transmission of signals introduced by IL-1ß and TNF- α are blocked by inhibiting the activity of sphingomyelinase using an inhibitor, the symptoms of various diseases related to cytokines can be improved. One would have a reasonable expectation of success since Chatterjee et al. provide a purified sphingomyelinase and Ausubel et al. provide time tested recombinant techniques that has been used by a number of other inventors. In addition Takao et al. or Malmqvist et al. provide a robust and time tested assay method wherein the cleavage target is immobilized on a solid support for ease of separation of cleaved products and Ogita et al. demonstrate the existence of a chemical compound which inhibits sphingomyelinase and their importance.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

Arguing against the above rejection applicant maintains that the references do not render the claim obvious. Applicant argues that pending claim 13 recites a step in which the sphingomyelinase cleavage target is bound to a solid support and claim 34 recites contact between the cleavage target, candidate agent, and enzyme and in view of these amendments the USPTO'S combination of references is not the claimed invention.

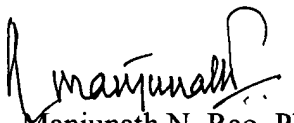
Applicant also argues that Chatterjee et al. as cited does not teach the step of binding the cleavage target to the solid support or using bound cleavage target at all and Ogita et al. or Ausbel et al. as relied on do not remedy this defect. Applicant argues that a worker reading the specification would see the clear advantages of binding the sphingomyelinase cleavage target to a solid support and using the same according to the claimed method. Applicant argues for instance, a wide variety of supports can be used and are compatible with binding to the cleavage target and that use of solid support to bind the cleavage target increases assay convenience (e.g., support can be stored until needed, see Example 2) etc. Applicant argues that none of such advantages are specifically taught or suggested by the USPTO'S combination of Chatterjee, Ausbel and Ogita.

While Examiner agrees that the previous combination of references did not teach the claimed invention, the instant combination of references render the claimed prima facie obvious. This is because the deficiencies of the combination of previous references is remedied by the new references of Takao et al. and or Malmqvist et al. These two references do teach the immobilization of the substrate on to a solid support in a sphingomyelinase assay and the Malmqvist et al. further teach the same advantages of immobilizing the substrate sphingomyelin, as that taught in the instant specification, i.e., the ease of handling and storage of immobilized lipid substrate. Therefore contrary to applicant's argument, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

December 13, 2005